

Side effects of long-term prophylaxis with attenuated androgens in hereditary angioedema: Comparison of treated and untreated patients

Marco Cicardi, MD, Roberto Castelli, MD, Lorenza C. Zingale, MD,
and Angelo Agostoni, MD *Milan, Italy*

Danazol and stanozolol, 17- α -alkylated attenuated androgens, prevent symptoms in hereditary angioedema (HAE), the inherited deficiency of C1-inhibitor.^{1,2} Possible side effects can be due to: (1) residual hormonal activity (seborrhoea, acne, increased hair growth, weight gain, deepening of the voice, decreased breast size, vasomotor symptoms, irregular vaginal bleeding, decreased libido), (2) 17 α -alkylation (hepatotoxicity, ranging from signs of necrosis and cholestasis to the induction of hepatocellular and vascular neoplasm), (3) changes in the levels of lipoproteins (possible potentiation of atherogenesis).^{3,4}

The few reports on the safety of long-term treatment with androgens for prophylaxis of HAE have failed to show important drug-related side effects.^{5,6} However, none of these studies included a control group of untreated patients with HAE.

The aim of this study was to compare clinical and biochemical parameters in patients with untreated HAE and in those who had been treated with attenuated androgens for long periods.

METHODS

We studied 24 men and 46 women with HAE. The diagnosis was based on personal and family history of recurrent angioedema symptoms and low levels of functional C1-inhibitor. Eight men and 28 women (age range, 22 to 74 years; median age, 44 years) had been receiving prophylactic treatment with attenuated androgens (danazol, stanozolol, or both in different periods). Fifteen men and 18 women (age range, 15 to 67 years; median age, 44 years) who had never received attenuated androgens or any other long-term prophylactic therapy served as control subjects. According to our policy, long-term prophylaxis is proposed only to patients with one or more angioedema attacks per month.² The treatment had lasted for a median of 125.5 months (range, 22 to 273 months). A transverse study was performed, and each patient had a physical examination, complete blood count, biochemical assessment of renal and hepatic function (plasma creatinine, electrolytes, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ -glu-

Abbreviations used

HAE: Hereditary angioedema

HCV: Hepatitis C virus

tamyl-transpeptidase, bilirubin, hepatitis B and C markers, and α -feto-protein), blood glucose, creatine kinase, cholesterol, coagulation test. For patients in the treated group, ultrasonography of the liver and spleen was performed.

The statistical analysis included the chi square test with Yates' correction and the Mann-Whitney nonparametric U test. A *p* value of less than 0.05 was considered a significant difference.

RESULTS

Five patients were treated only with danazol, 31 with danazol and stanozolol in different periods, and none with stanozolol only. The dose was established on a clinical basis as the minimal dose at which the patient remained nearly free of symptoms (i.e., 2 or fewer minor attacks per year). This daily dose ranged from 1 to 2 mg for stanozolol and from 50 to 200 mg for danazol. Two patients receiving stanozolol and six receiving danazol, although experiencing two to six minor attacks per year, preferred not to try higher doses.

Main side effects were menstrual irregularities (in 50% of premenopausal women with danazol and in 18% with stanozolol) and increase in body weight in both men and women (28% with danazol and 17% with stanozolol). These effects were dose-related. Nine patients (age range, 35 to 74 years; median age, 60 years) treated with danazol and stanozolol had arterial hypertension (diastolic pressure >95 mm Hg, systolic pressure >160 mm Hg). One of these patients had borderline values of hypertension (diastolic, 90 to 94 mm Hg; systolic, 141 to 159 mm Hg) before treatment and became hypertensive afterward. One control (untreated) subject also had hypertension. The numbers of patients with hypertension in the two groups were significantly different (chi square with Yates' correction, *p* = 0.02). Development of hypertension was not related to higher doses or longer treatment. The main clinical features recorded for treated patients are reported in Table I.

Plasma electrolyte, bilirubin, glucose, and α -feto-protein values and results of coagulation tests were normal in all patients. One subject in the treated group (with

From the Institute of Internal Medicine University of Milan, Istituto di Ricovero e Cura a Carattere Scientifico, Ospedale Maggiore.

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Reprint requests: Angelo Agostoni, MD, Istituto di Medicina Interna, Via Pace 15, 20122 Milano, Italy.

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TABLE I. Clinical features in 36 patients with HAE treated with attenuated androgens for long periods

Menstrual irregularities*	15
Gain in body weight	14
Acne	4
Arterial hypertension	9
Hypothyroidism	1
Myocardial infarction	1

*In 22 premenopausal women.

hypertension and myocardial infarction) had a 1.5-fold increase in creatinine. The other parameters showed slight abnormalities, with distribution between the two groups not statistically different as determined by the nonparametric test or by the chi square test (Table II). Hepatic function parameters were further analyzed to compare hepatitis C virus (HCV)-seropositive patients ($n = 11$) and HCV-seronegative patients ($n = 25$) within the treated group: no statistically significant differences were seen. In these patients ultrasound examinations demonstrated the presence of minor abnormalities that appeared to be randomly distributed with respect to the presence or absence of HCV infection. Three patients (2 HCV-seropositive and 1 HCV-seronegative) treated with attenuated androgens fulfilled the criteria for diagnosis of chronic hepatitis (increased alanine aminotransferase values for at least 6 months) and underwent liver biopsy. The histologic findings showed minimal changes in liver structure in all of these patients.

DISCUSSION

Attenuated androgens became the treatment of choice for severe HAE almost 20 years ago. Their extraordinary effectiveness changed the quality of life for patients with this disease. However, because the treatment may easily last throughout life (major contraindications are limited to childhood and pregnancy), their long-term toxicity needs to be continually assessed.

The data reported in this article suggest that stanozolol is slightly more effective than danazol, probably because its fewer side effects facilitate achievement of the appropriate dose. To investigate their toxicity, we performed a set of biochemical analyses, chosen to detect the disorders usually connected with the use of these drugs.⁴⁻⁶ The results were compared with those for a control group of patients with untreated HAE. Statistical analyses of the results demonstrated that attenuated androgens were not responsible for the pathologic changes in any of the parameters. The results of this study also suggest that signs of liver damage are not a feature of the long-term use of these drugs, even in patients with HCV infection. Such an infection is frequent in patients with HAE because of exposure to plasma derivatives for the treatment of acute attacks.⁷ Ultrasound examination, at present the test of choice for early diagnosis of hepatic masses, further supports our

TABLE II. Median values (and ranges) of laboratory parameters for patients with HAE: 36 receiving prophylactic treatment with attenuated androgens and 34 control subjects who never received prophylactic treatment

	Patients treated with androgens	Control subjects
ALT	32.5	19
(0-40 U/L)	(7-216)	(11-105)
AST	24	21
(0-37 U/L)	(15-113)	(13-89)
Alkaline phosphatase	180	177
(98-279 U/L)	(96-328)	(98-952)
Creatine kinase	92	99.5
(24-170 U/L)	(42-456)	(41-275)
Cholesterol	213	193.5
(<200 mg/dl)	(119-302)	(141-289)
Na ⁺	139	139
(135-145 mmol/L)	(133-145)	(133-143)
K ⁺	4.3	4.2
(3.5-5.0 mmol/L)	(3.2-5.1)	(3.6-4.8)
BUN	32	35
(18-50 mg/dl)	(24-59)	(23-60)
Plasma creatinine	0.83	0.9
(0.5-1.4 mg/dl)	(0.53-2.0)	(0.6-1.26)

ALT, Alanine aminotransferase; BUN, blood urea nitrogen.

early report⁸ that liver tumors are not present in patients with HAE receiving long-term treatment with attenuated androgens.

An unexpected result of our study was the presence of arterial hypertension in a notable number (25%) of treated patients, compared with only one patient (3%) in the control group. The fact that the two groups were age-matched and that there were more men in the control group adds further importance to this finding. A previous study performed in 60 patients with HAE who were treated with these drugs demonstrated that 10% of them had hypertension.⁶ In our patients hypertension developed after either a few months (3 cases) or several years (5 cases) of treatment. Control of arterial pressure was obtained with β -blockers (1 case), calcium channel blockers (4 cases), and diuretics (3 cases). One patient refused specific treatment. Angiotensin-converting enzyme inhibitors, which increase the half-life of bradykinin, precipitate symptoms in patients with HAE, and thus they were avoided. C1-inhibitor deficiency per se facilitates bradykinin release, and bradykinin appears to be the main mediator of vasopermeability in HAE.⁹ Because bradykinin has a hypotensive effect,¹⁰ it could protect patients with HAE from hypertension: in this case attenuated androgens would act against such protection. Along with hypertension, treated patients also had higher (although not significantly) cholesterol levels and increased body weight, which emphasizes the need for further multicenter studies to assess the atherogenic risk of long-term treatment with attenuated androgens in patients with HAE.

In general, we believe that physicians will never feel totally confident prescribing treatments to be continued throughout life. For this reason, in the case of HAE, a disease only episodically symptomatic, availability of a safe and easy-to-use drug able to reverse attacks is the final goal. Effective blockers of bradykinin receptors, which have recently started to be studied in human beings, appear to be a promising approach to treatment of HAE attacks.¹¹

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